NOVARTIS

AZARGA (brinzolamide/timolol maleate)

brinzolamide 10 mg/ml / timolol 5 mg/ml eye drops suspension

Professional Information

Document status: Final

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SCHEDULING STATUS **S4**

PROPRIETARY NAME AND DOSAGE FORM

AZARGA, eye drops, suspension

COMPOSITION

1 ml of suspension contains 10 mg brinzolamide and 5 mg timolol (as timolol maleate).

Preservative: benzalkonium chloride 0,01 % (w/v).

Preservative aid: disodium edetate 0,01 % (w/v).

Excipients: carbomer 974P, mannitol, sodium chloride, tyloxapol and purified water.

Contains sugar (mannitol).

PHARMACOLOGICAL CLASSIFICATION

A 15.4 Ophthalmic preparations, other

ATC code: S01ED51

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

Mechanism of action

AZARGA contains two active substances: brinzolamide and timolol maleate. These two components decrease elevated intra-ocular pressure primarily by reducing aqueous humour secretion, but do so by different mechanisms of action.

The combined effect of these two medicines results in additional intra-ocular pressure reduction compared to either compound alone. Brinzolamide is a potent inhibitor of human carbonic anhydrase II (CA-II), the predominant iso-enzyme in the eye. Inhibition of carbonic anhydrase in the ciliary processes of the eye decreases aqueous humour secretion, presumably by slowing the formation of bicarbonate ions with subsequent reduction in sodium and fluid transport.

Timolol is a non-selective beta-adrenergic blocking medicine that has no intrinsic sympathomimetic, direct myocardial depressant or membrane-stabilising activity. Tonography and fluorophotometry studies in man suggest that its predominant action is related to reduced aqueous humour formation and a slight increase in outflow facility.

Pharmacokinetic properties

Absorption

Following topical ocular administration, brinzolamide and timolol are absorbed through the cornea and into the systemic circulation. In a pharmacokinetic study, healthy subjects received oral brinzolamide (1 mg) twice daily for 2 weeks to shorten the time to reach steady-state prior to the start of AZARGA administration.

Following twice daily dosing of AZARGA in both eyes for 13 weeks, red blood cell (RBC) concentrations of brinzolamide averaged 18,8 ± 3,29 µM, 18,1 ± 2,68 µM and 18,4 ± 3,01 µM at weeks 4, 10 and 15, respectively, indicating that steady-state RBC concentrations of brinzolamide were maintained. At steady state, following administration of AZARGA, the mean plasma C_{max} and AUC_{0-12h} of timolol were 27 % and 28 % lower (C_{max}: 0,824 ± 0,453 ng/ml; AUC_{0-12h}: 4,71 ± 4,29 ng h/ml), respectively, in comparison to the administration of timolol 5 mg/ml (C_{max}:1,13 ± 0,494 ng/ml; AUC_{0-12h}: 6,58 ± 3,18 ng h/ml). The lower systemic exposure to timolol following AZARGA administration is not clinically relevant. Following administration of AZARGA, mean C_{max} of timolol was reached at 0,79 ± 0,45 hours.

Distribution

Plasma protein binding of brinzolamide is moderate (about 60 %). Brinzolamide is sequestered in RBCs due to its high affinity binding to CA-II and to a lesser extent to CA-I. Its active N-desethyl metabolite also accumulates in RBCs where it binds primarily to CA-I. The affinity of brinzolamide and metabolite to RBC and tissue CA results in low plasma concentrations.

Ocular tissue distribution data in rabbits showed that timolol can be measured in aqueous humour up to 48 hours after administration of AZARGA. At steady state, timolol is detected in human plasma for up to 12 hours after administration of AZARGA.

Metabolism

The metabolic pathways for the metabolism of brinzolamide involve N-dealkylations, O-dealkylations and oxidation of its N-propyl side chain. N-desethyl brinzolamide is a major metabolite of brinzolamide formed in humans, which also binds to CA-I in the presence of brinzolamide and accumulates in RBCs. In vitro studies show that the metabolism of brinzolamide mainly involves CYP3A4 as well as at least four other isozymes (CYP2A6, CYP2B6, CYP2C8 and CYP2C9).

Timolol is metabolised by two pathways. One route yields an ethanolamine side chain on the thiadiazole ring and the other giving an ethanolic side chain on the morpholine nitrogen and a second similar side chain with a carbonyl group adjacent to the nitrogen. Timolol metabolism is mediated primarily by CYP2D6.

Excretion

Brinzolamide is eliminated primarily by renal excretion (approximately 60 %). About 20 % of the dose has been accounted for in urine as metabolite. Brinzolamide and N-desethyl-brinzolamide are the predominant components found in the urine along with trace levels (< 1 %) of the N-desmethoxypropyl and O-desmethyl metabolites.

Timolol and its metabolites are primarily excreted by the kidneys. Approximately 20 % of a timolol dose is excreted in the urine unchanged and the remainder excreted in urine as metabolites. The plasma $t_{1/2}$ of timolol is 4,8 hours after administration of AZARGA.

INDICATIONS

Decrease of intraocular pressure (IOP) in adult patients with open-angle glaucoma or ocular hypertension for whom monotherapy provides insufficient IOP reduction.

CONTRAINDICATIONS

- Hypersensitivity to brinzolamide, timolol, or to any of the excipients.
- Reactive airway disease including bronchial asthma or a history of bronchial asthma, or severe chronic obstructive pulmonary disease.
- Sinus bradycardia, sick sinus syndrome, sino-atrial block, second or third degree atrioventricular block, overt cardiac failure, or cardiogenic shock.
- Severe allergic rhinitis and bronchial hyper-reactivity; hypersensitivity to other beta-blockers.
- Hyperchloraemic acidosis (see Dosage and directions for use).

- Severe renal impairment.
- Hypersensitivity to sulphonamides (see Warnings and Special Precautions).
- Pregnancy and lactation.

WARNINGS AND SPECIAL PRECAUTIONS

General

Brinzolamide and timolol, as in AZARGA are absorbed systemically. Due to the beta-adrenergic component, timolol, the same types of cardiovascular, pulmonary and other adverse reactions seen with systemic beta-adrenergic blocking medicines may occur.

Hypersensitivity reactions can occur in patients receiving AZARGA as it is absorbed systemically. If signs of serious reactions or hypersensitivity occur, discontinue the use of this product.

Acid-base disturbances have been reported with oral carbonic anhydrase inhibitors, such as AZARGA. Use with caution in patients with risk of renal impairment because of the possible risk of metabolic acidosis.

The possible role of brinzolamide, as in AZARGA on corneal endothelial function has not been investigated in patients with compromised corneas (particularly in patients with low endothelial cell count).

Careful monitoring of patients with compromised corneas, such as patients with diabetes mellitus or corneal dystrophies, is recommended.

Cardiac disorders

In patients with cardiovascular diseases (e.g. coronary heart disease, Prinzmetal's angina and cardiac failure) and hypotension, therapy with beta-blockers, such as timolol in AZARGA, should be critically assessed and the therapy with other medicines should be considered. Patients with cardiovascular diseases should be watched for signs of deterioration of these diseases and of adverse reactions.

Cardiac failure should be adequately controlled before beginning therapy with timolol in AZARGA.

Vascular disorders

Patients with severe peripheral circulatory disturbance/disorders (i.e. severe forms of Raynaud's disease or Raynaud's syndrome) should be treated with caution.

Respiratory disorders

Respiratory reactions, including death due to bronchospasm in patients with asthma have been reported following administration of some ophthalmic beta-blockers such as timolol maleate in AZARGA.

Hypoglycaemia/diabetes

Beta-adrenergic blocking medicines, such as timolol in AZARGA, should be administered with caution in patients subject to spontaneous hypoglycaemia or to patients with labile insulin-dependent diabetes, as AZARGA may mask the signs and symptoms of acute hypoglycaemia.

Hyperthyroidism

Beta-blockers, such as timolol in AZARGA, may also mask the signs of hyperthyroidism.

Muscle weakness

Beta-adrenergic blocking medicines, such as timolol in AZARGA, have been reported to potentiate muscle weakness consistent with certain myasthenic symptoms (e.g. diplopia, ptosis and generalized weakness).

Anaphylactic reactions

While taking beta-adrenergic blocking medicines, such as timolol in AZARGA, patients with a history of atopy or a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge with such allergens and unresponsive to the usual doses of epinephrine (adrenaline) used to treat anaphylactic reactions.

Choroidal detachment

Choroidal detachment has been reported with administration of aqueous suppressant therapy (e.g. timolol in AZARGA) after filtration procedures.

Surgical anaesthesia

Beta-blocking ophthalmological preparations such as AZARGA may block systemic beta-agonist effects e.g. of epinephrine (adrenaline). The anaesthesiologist should be informed when the patient is receiving timolol, as in AZARGA.

Other beta-blocking medicines

Timolol, as in AZARGA, may interact with other medicines (see INTERACTIONS). The effect on intraocular pressure or the known effects of systemic beta-blockade may be potentiated when AZARGA is given to patients already receiving a systemic oral beta-adrenergic blocking medicine. The use of two topical beta-adrenergic blocking medicines or two local carbonic anhydrase inhibitors is not recommended.

Ocular effects

There is limited experience with AZARGA in the treatment of patients with pseudoexfoliative glaucoma or pigmentary glaucoma. Caution should be utilised in treating these patients and close monitoring of IOP is recommended.

AZARGA has not been studied in patients with narrow-angle glaucoma and its use is not recommended in these patients.

AZARGA is not recommended for use in children below 18 years due to lack of data on safety and efficacy.

Contact lenses

Specifically, patients wearing contact lenses have not been studied and careful monitoring of these patients when using brinzolamide, as in AZARGA, is recommended, since carbonic anhydrase inhibitors may affect corneal hydration and wearing contact lenses might increase the risk for damage to the cornea.

Benzalkonium chloride, which is commonly used as a preservative in ophthalmic products, has been reported to cause punctate keratopathy and/or toxic ulcerative keratopathy. Since AZARGA contains benzalkonium chloride, close monitoring is required with frequent or prolonged use.

Benzalkonium chloride, in AZARGA, may cause eye irritation and is known to discolour soft contact lenses. Contact with soft contact lenses is to be avoided. Patients must be instructed to remove contact lenses prior to the application of AZARGA and wait 15 minutes after instillation of the dose before reinsertion.

Effects on ability to drive and use machines

Oral carbonic anhydrase inhibitors, such as brinzolamide in AZARGA, may impair the ability to perform tasks requiring mental alertness and / or physical coordination.

Temporary blurred vision or other visual disturbances may affect the ability to drive or use machines. If blurred vision occurs at instillation, the patient must wait until vision clears before driving or using machinery.

INTERACTIONS

No interaction studies have been performed.

AZARGA contains brinzolamide, a carbonic anhydrase inhibitor and, although administered topically, is absorbed systemically. Acid-base disturbances have been reported with oral carbonic anhydrase inhibitors. The potential for interactions must be considered in patients receiving brinzolamide in AZARGA.

There is potential for an additive effect on the known systemic effects of carbonic anhydrase inhibition in patients receiving an oral carbonic anhydrase inhibitor and AZARGA. The concomitant administration of AZARGA and oral carbonic anhydrase inhibitors has not been studied and is not recommended.

The cytochrome P-450 isozymes responsible for metabolism of brinzolamide include CYP3A4 (main), CYP2A6, CYP2B6, CYP2C8 and CYP2C9. It is expected that inhibitors of CYP3A4 such as ketoconazole, itraconazole, clotrimazole, ritonavir and troleandomycin will inhibit the metabolism of brinzolamide by CYP3A4. Caution is advised if CYP3A4 inhibitors are given concomitantly. However, accumulation of brinzolamide in AZARGA is unlikely as renal elimination is the major route. Brinzolamide is not an inhibitor of cytochrome P-450 isozymes.

There is a potential for additive effects resulting in hypotension and/or marked bradycardia when eye drops like AZARGA with timolol are administered concomitantly with oral calcium channel blockers,

guanethidine or beta-adrenergic blocking medicines, antidysrhythmics (including amiodarone), digoxin or parasympathomimetics.

The hypertensive reaction to sudden withdrawal of clonidine can be potentiated when taking beta-adrenergic blocking medicines.

Potentiated systemic beta-blockade (e.g. decreased heart rate, depression) has been reported during combined treatment with CYP2D6 inhibitors (e.g. quinidine, fluoxetine, paroxetine, cimetidine) and timolol, as in AZARGA.

Timolol may increase the hypoglycaemic effect of antidiabetic medicines.

Timolol can mask the signs and symptoms of hypoglycaemia (see WARNINGS AND SPECIAL PRECAUTIONS).

Mydriasis resulting from concomitant use of ophthalmic beta-blockers and epinephrine (adrenaline) has been reported occasionally.

PREGNANCY AND LACTATION

Safety and efficacy have not been established.

Pregnancy

There are no adequate data from the use of brinzolamide and timolol, as in AZARGA, in pregnant women. Studies in animals with brinzolamide have shown reproductive toxicity following systemic administration. The potential risk for humans is unknown.

Epidemiological studies with systemic use of beta-adrenergic blocking medicines have not revealed malformative effects, but show a risk for intra uterine growth retardation when beta-blockers are administered by the oral route. In addition, signs and symptoms of beta-blockade (e.g. bradycardia, hypotension, respiratory distress and hypoglycaemia) have been observed in the neonate when beta-blockers have been administered until delivery.

AZARGA should not be used during pregnancy. However, if AZARGA is administered until delivery, the neonate should be carefully monitored during the first days of life.

Lactation

It is not known whether ophthalmic administered brinzolamide is excreted in human breast milk. Animal studies have shown that following oral administration brinzolamide is excreted in human breast

milk. Timolol is excreted in breast milk having the potential to cause serious undesirable effects in the breastfeeding infant. As timolol does appear in human breast milk, breastfeeding mothers should not be treated with AZARGA.

DOSAGE AND DIRECTIONS FOR USE

For ocular use.

Use in adults, including the elderly

The dose is one drop of AZARGA in the conjunctival sac of the affected eye(s) twice daily.

Nasolacrimal occlusion or gently closing the eyelid for 2 minutes after instillation is recommended. This may reduce the systemic absorption of medicinal products administered via the ocular route and result in a decrease in systemic adverse reactions and an increase in local activity.

If more than one topical ophthalmic medicine is being used, the medicines must be administered at least 5 minutes apart.

If a dose is missed, treatment should be continued with the next dose as planned. The dose should not exceed one drop in the affected eye(s) twice daily.

When substituting another ophthalmic antiglaucoma medicine with AZARGA, the other medicine should be discontinued and AZARGA should be started the following day.

Paediatric patients

AZARGA is not recommended for use in children below 18 years due to a lack of data on safety and efficacy.

Use in hepatic and renal impairment

No studies have been conducted with AZARGA or with timolol 5 mg/ml eye drops in patients with hepatic or renal impairment. No dosage adjustment is necessary in patients with hepatic impairment or in patients with mild to moderate renal impairment.

Brinzolamide, as in AZARGA, has not been studied in patients with severe renal impairment (creatinine clearance < 30 ml/min) or in patients with hyperchloraemic acidosis. Since brinzolamide

and its main metabolite are excreted predominantly by the kidney, AZARGA is contraindicated in patients with severe renal impairment (see CONTRAINDICATIONS).

Instruct patients to shake the bottle well before use.

To prevent contamination of the dropper tip and solution, care must be taken not to touch the eyelids, surrounding areas or other surfaces with the dropper tip of the bottle. Instruct patients to keep the bottle tightly closed when not in use.

SIDE EFFECTS

In two clinical trials of 6 and 12 months duration involving 394 patients treated with AZARGA, the most frequently reported adverse reaction was transient blurred vision (3,6 %) upon instillation, lasting from a few seconds to a few minutes.

Dysgeusia (bitter or unusual taste in the mouth following instillation) was a frequently reported systemic undesirable effect associated with the use of AZARGA during clinical studies. It is likely caused by passage of the eye drops in the nasopharynx via the nasolacrimal canal and is attributable to brinzolamide.

AZARGA contains brinzolamide which is a sulphonamide inhibitor of carbonic anhydrase with systemic absorption. Gastrointestinal, nervous system, haematological, renal and metabolic effects are generally associated with systemic carbonic anhydrase inhibitors. The same type of undesirable effects that are attributable to oral carbonic anhydrase inhibitors may occur with topical administration.

Tabulated summary of adverse reactions:

The following adverse reactions are classified according to the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); or very rare (< 1/10 000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System Organ Classification	**MedDRA Preferred Term (v. 14.1)**
Psychiatric disorders	*Uncommon*: insomnia
Nervous system disorders	*Common*: dysgeusia

Eye disorders	*Common*: blurred vision, eye irritation, eye pain, *Uncommon*: corneal erosion, punctate keratitis, dry eye, eye discharge, eye pruritus, ocular hyperaemia, blepharitis, allergic conjunctivitis, corneal disorder, anterior chamber flare, conjunctival hyperaemia, eyelid margin crusting, asthenopia, abnormal sensation in eye, eyelids pruritus, allergic blepharitis, erythema of eyelid, foreign body sensation in eyes,
Vascular disorders	*Uncommon*: decreased blood pressure
Respiratory, thoracic and mediastinal disorders	*Uncommon*: chronic obstructive pulmonary disease, pharyngolaryngeal pain, cough, rhinorrhoea
Skin and subcutaneous tissue disorders	*Uncommon*: hair disorder, lichen planus

AZARGA contains brinzolamide and timolol (as timolol maleate). Additional adverse reactions associated with the use of the individual components observed in clinical trials and postmarketing experience that may potentially occur with AZARGA include:

	Brinzolamide 10 mg/ml	**Timolol 5mg/ml**
Infections and infestations	nasopharyngitis, pharyngitis, sinusitis, rhinitis	
Blood and lymphatic system disorders	red blood cell count decreased, blood chloride increased	
Immune system disorders	hypersensitivity	
Metabolism and nutrition disorders		hypoglycaemia
Psychiatric disorders	apathy, depression, depressed mood, libido decreased, nightmare, nervousness	depression

Nervous system disorders	somnolence, motor dysfunction, amnesia, memory impairment, dizziness, paraesthesia, tremor, headache, hypoaesthesia, ageusia	cerebral ischaemia, cerebrovascular accident, syncope, myasthenia gravis, paraesthesia, headache, dizziness
Eye disorders	keratitis, keratopathy, increased optic nerve cup/disc ratio, corneal epithelium defect, corneal epithelium disorder, increased intraocular pressure, eye deposit, corneal staining, corneal oedema, conjunctivitis, meibomianitis, diplopia, glare, photophobia, photopsia, reduced visual acuity, pterygium, ocular discomfort, keratoconjunctivitis sicca, hypoaesthesia of the eye, scleral pigmentation, subconjunctival cyst, increased lacrimation, visual disturbance, eye swelling, eye allergy, madarosis, eyelid disorder, eyelid oedema	diplopia, eyelid ptosis, conjunctivitis, keratitis, visual disturbance
Ear and labyrinth disorders	tinnitus, vertigo	
Cardiac disorders	cardio-respiratory distress, angina pectoris, bradycardia, irregular heart rate, dysrhythmia, palpitations, tachycardia, increased heart rate	cardiac arrest, cardiac failure, dysrhythmia, atrioventricular block, bradycardia, palpitations
Vascular disorders	Increased blood pressure, hypertension	hypotension
Respiratory, thoracic and mediastinal disorders	dyspnoea, asthma, bronchial hyperactivity, epistaxis, throat irritation, nasal congestion, upper respiratory tract congestion, postnasal drip, sneezing, nasal dryness	respiratory failure, bronchospasm, dyspnoea, nasal congestion
Gastrointestinal disorders	dry mouth, oesophagitis, vomiting, diarrhoea, nausea, dyspepsia, upper abdominal pain, abdominal discomfort, stomach discomfort, frequent bowel movements, gastrointestinal disorder, oral hypoaesthesia, oral paraesthesia, flatulence	diarrhoea, nausea
Hepatobiliary disorders	abnormal liver function test	

Skin and subcutaneous tissue disorders	urticaria, maculo-papular rash, rash, generalised pruritus, alopecia, skin tightness, dermatitis, erythema	alopecia, rash
Musculoskeletal and connective tissue disorders	back pain, muscle spasms, myalgia, arthralgia, pain in extremity	
Renal and urinary disorders	renal pain, pollakiuria	
Reproductive system and breast disorders	erectile dysfunction	
General disorders and administrative site conditions	pain, asthenia chest discomfort, , fatigue, feeling abnormal, feeling jittery, irritability chest pain, peripheral oedema, malaise, medication residue	asthenia, chest pain
Injury, poisoning and procedural complications	foreign body in eye	

Additional adverse reactions identified from post-marketing surveillance include the following. Frequencies cannot be estimated from the available data.

System Organ Classification	**MedDRA Preferred Term (v. 14.1)**
Immune system disorders	Hypersensitivity
Psychiatric disorders	Depression
Nervous system disorders	Dizziness, headache
Eye disorders	Eyelid oedema, visual impairment
Vascular disorders	Blood pressure increased
Respiratory, thoracic and mediastinal	Dyspnoea, epistaxis
Gastrointestinal disorders	Abdominal pain upper, diarrhoea, dry mouth, nausea
Skin and subcutaneous tissue disorders	Alopecia, erythema, rash

Musculoskeletal and connective tissue disorders	Myalgia
General disorders and administration site conditions	Chest pain, fatigue

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS

TREATMENT

If overdose with AZARGA eye drops occurs, treatment should be symptomatic and supportive. In case of accidental ingestion, symptoms of overdose from beta blockade may include bradycardia, hypotension, cardiac failure and bronchospasm.

Due to brinzolamide in AZARGA, electrolyte imbalance, development of an acidotic state, and possibly central nervous system effects may occur. Serum electrolyte levels (particularly potassium) and blood pH levels should be monitored. Studies have shown that timolol does not dialyse readily.

IDENTIFICATION

White to off-white uniform suspension.

PRESENTATION

Round opaque low density polyethylene bottles with a dispensing plug and white polypropylene screw cap containing 5 ml suspension, packaged inside an outer carton.

STORAGE INSTRUCTIONS

Keep out of reach and sight of children.

Discard 4 weeks after opening.

Store in a cool, dry place at or below 30 °C.

REGISTRATION NUMBER

44 /15.4/0046

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

Novartis South Africa (Pty) Ltd

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DATE OF PUBLICATION OF THE PACKAGE INSERT

The date on the registration certificate of the medicine

02 March 2012

The date of the most recently revised package insert as approved by Council

20 March 2018